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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,169	06/08/2001	Clemens Antoni Van Blitterswijk	04148-00012	9604

7590 06/29/2004

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EXAMINER

DEBERRY, REGINA M

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 06/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,169	VAN BLITTERSWIJK ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10,13,14,16-18,20-23,25,26 and 28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10,13,14,16-18,20-23,25,26 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Status of Application, Amendments and/or Claims

The amendment filed 14 April 2004 has been entered in full.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 10, 13, 14, 16-18, 20-23, 25, 26 and 28 are under examination.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

Claims 10, 13, 14, 16-18, 20-23 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of producing osteocalcin comprising the steps of

- (a) applying bone marrow cells on a substrate
 - (b) contacting the bone marrow cells with a culture medium
 - (c) inducing the bone marrow cells to differentiate into osteogenic tissue by one or more inductors of differentiation, wherein osteogenic tissue produce osteocalcin
 - (d) recovering osteocalcin from the culture medium,
- does not reasonably provide enablement for:
- a method of producing active factors (or bone growth factor) comprising the steps of
- of
- (a) applying undifferentiated mammalian cells on a substrate
 - (b) contacting the undifferentiated mammalian cells with a culture medium
 - (c) inducing the undifferentiated mammalian cells to differentiate by one or more

inductors of differentiation, wherein differentiated cells produce active factors (or bone growth factors)

(d) recovering the active factors (or bone growth factors) from the culture medium.

The basis for this rejection is set forth at pages 2-5 of the previous Office Action (14 January 2004).

Applicant argues that the instant specification provides considerable direction and guidance to make and use the claimed invention. Applicant states that the steps in the instant claims uses techniques that are well known by those of skill in the art in fields such as cell culture, cell biology, transplantation and the like. Applicant argues that several working examples were provided wherein undifferentiated cells were added to a substrate in the presence of culture medium and the cells are induced to differentiate and wherein active factors are recovered. Applicant cites Examples 1-4 from the instant specification. Applicant maintains that one of skill in the art would be able to use a variety of undifferentiated cells; as methods of inducing many kinds of undifferentiated mammalian cells to differentiate were well known at the time of filing. Applicant cites Biesecker *et al.* (Appendix A) and Cumano *et al.* (Appendix B). Applicant submits that one skill in the art could practice the claimed invention using a variety of cells, using methods known in the art at the time of filing. Applicant argues that factors could be isolated using a variety of methods known in the art. Applicant submits that determining whether a factor is active could be easily achieved by assaying for a

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specific cell morphology in the presence of the factor. Applicant cites the submitted references.

Applicants' arguments have been fully considered but not deemed persuasive for the following reasons. Examples 1-4 from the instant specification teach that rat bone marrow cultured in medium develop into opaque, three dimensional mineralized nodular structures after two weeks (page 5, lines 1-16). The specification states that the osteogenic character of rat bone marrow culture system has been well characterized using a number of criteria (page 5, lines 21-34). The specification teaches that the osteocalcin bone protein is released in the medium (page 6, lines 4-5 and page 12, lines 15-16). Thus, the specification teaches that bone marrow cells supplemented with media differentiated into osteoclast, which produced osteocalcin bone protein. Contrary to Applicant's assertion, there is no correlation between the working examples and the instant claims. The instant claims are broadly drawn to "any" cell proliferation, cell adhesion and/or bone formation factor. The instant claims are broadly drawn to "any" undifferentiated mammalian cell and "any" differentiated cell. The specification is not enabling for these limitations. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

The references submitted by Applicant are not found persuasive because the instant claims encompass a genus (undifferentiated mammalian cells, active factors and differentiated cells) and the submitted references teach specific species. Biesecker *et al.* use the *in vitro* differentiation potential of embryonic stem cells to clone partial cDNA that encode for alleged developmental growth factors. Embryonic stem cells

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differentiated into cystic embryoid bodies (CEB) containing primitive blood islands (PBI). RNA from CEBs was reverse transcribed and the partial cDNA sequences were entered and compared to known DNA sequence in GenBank. The sequences were designated as putative protein kinases because of sequence similarities to the protein kinase family. However, confirmation of kinase activity (via tyrosine or serine/threonine assays) or any type of biological activity (bone formation, proliferation or growth factor activity) was not verified by Biesecker *et al.* Cumano *et al.* teach the differentiation of B-lymphocytes from B cell progenitors. Cumano *et al.* do not teach the recovery of growth factors. Undue experimentation is a conclusion reached by weighing all of the Wands factor. A considerable amount of time is permissible for the quantity of experimentation needed to make or use the invention, if it's merely routine or if the skilled artisan is given sufficient direction or guidance. In the instant case, the experimentation is not routine and Applicant has failed to provide any guidance. The specification lacks working examples, which correlate with the instant claims. The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. However, the instant claims are so broad with respect to the disclosure that undue experimentation would be required of the skilled artisan. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

Claims 25, 26, 28 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The basis for this rejection is set forth at pages 5-6 of the previous Office Action (14 January 2004).

Applicant argues that stromal cells are bone marrow cells and directs the Examiner's attention to page 2, lines 23-24 of the specification. Applicant submits that since they teach the use of bone marrow cells in the claimed method and since stromal cells are bone marrow cells, it logically follows that Applicants teach the use of stromal cells in the claimed method.

Applicant's arguments have been fully considered but not deemed persuasive. The Examiner is familiar with stromal cells supporting *in vitro* development and/or differentiation, but is not familiar with stromal cells actually differentiating into a different cell. For instance, Cumano *et al.* (reference submitted by Applicant) teach the seeding of B-cell progenitors in the presence of stromal cells derived from bone marrow (S17 stromal cells). Furthermore, stromal cells are connective tissue cells of an organ found in the loose connective tissue. Stromal cells can be isolated from bone marrow, thyroid, ovary, etc. Thus bone marrow cell can comprise stromal cells. The Examiner has provided the definition of stromal cells from the On-line Medical Dictionary (Appendix A) and Dorland's Illustrated Medical Dictionary (Appendix B). The instant claims encompass "any" stromal cell. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

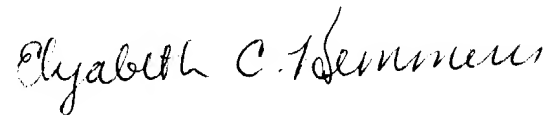
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



RMD
6/3/04



ELIZABETH KEMMERER
PRIMARY EXAMINER